Microbiota, obesity and insulin resistance

ADDENDUM

Valorization

The prevalence of obesity has reached epidemic proportions, and affects all ages and socioeconomic groups in the Western world[1,2]. In 2014, 13.1% of men and 19.9% of all women were overweight or obese. This worldwide obesity prevalence is expected to reach 18% in men and to surpass 21% in women in 2025. The excessive accumulation of body fat in the overweight and obese state increases the risk for the development of type 2 diabetes mellitus[3], cardiovascular disease, mental disorders[4] and several types of cancer[5]. The WHO Global Report on Diabetes 2016 showed that the total burden of deaths from high blood glucose has been estimated 3.7 million, including 1.5 million deaths due to diabetes alone. Yet, the rising obesity prevalence is also observed in many low- and middle-income countries. For example, Africa, which is home to 54 low- and middle-income countries, is expected to have the world's largest increase in the death rate caused by chronic diseases over the next decade[6].

The increasing worldwide prevalence of obesity and related cardiometabolic complications has a considerable economic and social impact. Health care costs include an expensive array of treatments. To delay disease progression, millions of individuals depend on medication and surgery to treat obesity-related complications. For example, medication to lower cholesterol, blood pressure and blood glucose, gastric bypass surgery or cardiovascular surgery. Despite improved medical and technological advances, a downward trend in longevity has been observed that is related to the increased incidence of obesity[7]. Moreover, this decrease in life expectancy might only accelerate in the future, since the current generation of children has a higher BMI and prevalence of related complications than ever before[1].

It is therefore important to implement new strategies to improve worldwide health and awareness of the problems that come along with being overweight and obese. For years, the public health approach to obesity was the advice to consume less and exercise more. However, attempts to lower body mass for a longer time period without the implementation of a healthy lifestyle in daily life and without addressing biological drivers of weight gain, inevitably fails for the majority of people. Therefore, better knowledge on weight loss strategies, healthy dietary components, and parameters of human metabolism as well as the triggers that may give lead to implementation of a healthy lifestyle are needed and warrant a close collaboration between research, industry and the government.

Research

The balance between energy intake, energy expenditure and energy excretion is maintained by a large regulatory network between metabolic organs. There is close interaction between the adipose tissue, skeletal muscle, pancreas and the liver in the regulation of energy and substrate metabolism. Studies performed over the last decade have indicated that the bacteria residing in the intestinal tract are part of this inter-organ crosstalk. Perturbations of microbial populations may contribute to an obesogenic phenotype, inflammation, alterations in glucose metabolism and insulin resistance. Importantly, however, mechanistic studies almost exclusively have been performed in rodents, and results from these studies cannot directly be used to optimize public health guidelines. This thesis describes a clinical trial in overweight and obese humans to better understand if and how specific microbial populations may contribute to the development of obesity and related metabolic and inflammatory perturbations, thereby making scientific knowledge suitable and available for societal or economic utilization. Our findings demonstrate that pronounced modulation of the gut microbiota composition did not significantly affect host metabolism. Even after eight weeks follow-up, when the microbiota composition was still considerably altered as compared to baseline, no significant differences in host metabolism were found. The extrapolation of findings from animal studies to relevance for humans is an important step in the process of valorization. Knowledge on the effect of microbiota manipulation in humans may provide useful information to develop and/or optimize (nutritional or lifestyle-related) strategies to prevent obesity and obesity-related metabolic disturbances. Moreover, the studies described in this thesis provide new perspectives for future research and suggestions for improvement of intervention protocols to further investigate the link between microbiota and human metabolism. For example, since we found large inter-individual differences in the gut microbiota composition and the relationship with metabolic phenotype, this suggests that dietary interventions may need to be more personalized. In addition, future studies may consider inclusion of a lean, metabolically healthy control group. Finally, it is important that future studies include both men and women, since increasing evidence indicates gender differences in physiology, microbiota composition and sex hormones regarding the susceptibility to intervention effects.

Industry

The research as described in the present thesis was part of an interdisciplinary collaboration between academia, industry, and government within the framework of the Top Institute Food and Nutrition (TIFN). The ambition of this private-public partnership is to provide the knowledge base that is needed for high-impact innovations in food and nutrition. The motto 'scientific excellence, industrial relevance' indicates the importance of valorization within TIFN. The close collaboration between industry and academia leads to demand-driven research, which might provide long-term business strategies. Although the industrial partners had no leading role in the design of this study, their critical questions and suggestions were taken into account to optimize the study design.
The goal of the study as described in this thesis was to provide the nutritional industry with insights in the importance of the intestinal microbiome in obesity and related metabolic impairments. The fact that we were not able to confirm a clear relationship between the gut microbiota and metabolic health parameters in an overweight/obese population shows that the human organism and its interaction with the environment is extremely complex. Inter-individual differences in lifestyle, diet, country of origin, mode of delivery at birth, medical history, travel habits and cultural habits make it hard to determine the exact role of the microbiome in obesity and comorbidities. Long term, moderate alterations of the microbiota composition (e.g. by prebiotics or probiotics) might be needed to obtain health benefits, if the gut microbiota appears to contribute to metabolic health in humans.

Government

The government may take measures to make the implementation of a healthy lifestyle more feasible, such as taxes on unhealthy products, creating an environment that stimulates physical activity, and the implementation of a healthy lifestyle into health care prevention. The studies described in this thesis are an important first step in elucidating the importance of the gut microbiota in host metabolism in humans, but do not provide the government with direct advice to change policy on guidelines for healthy nutrition. However, these studies show that we are still in an early phase regarding microbiota research, and governmental funding in this area of research remains important to answer a broad range of new questions.

Health care professionals

Although the results of the studies as described in this thesis show that microbiota manipulation by seven days antibiotics treatment does not affect human metabolism, the use of antibiotics should be decreased in common practice because of rising antibiotics resistance worldwide. In addition to the increasing problems regarding antbiotics resistance, it has been demonstrated that the risk of developing type 2 diabetes was increased when subjects have been exposed to >5 antibiotic treatments[8]. Moreover, the number of prescriptions and duration of antibiotic treatment may accelerate the ageing-related decline of intestinal integrity[9]. Health care professionals play an important role in encouraging healthy behavior and should provide dietary guidelines to obese patients, involving improved quality of food. The results of the studies described in this thesis do not provide direct guidelines for health care, but indicate that the promising animal data in the field of the gut microbiome generated and published over the last decade, including fecal transplantation data, should be critically evaluated and requires more studies in humans before developing or implementing treatment strategies for common practice.

General public

When it comes to trust the information that is provided to the general public, scientists appear to be the most trusted, whereas the least trusted group consists of politicians[10]. It is for the scientific community therefore extremely important to provide the general public with clear and understandable information regarding study results. The overwhelming load of information about 'healthy' and 'dangerous' food in the news and social media, often provides people with the wrong information and lifestyle advice. Moreover, the interpretation of scientific results by journalists often needs more consideration.

This thesis shows for the first time that care should be taken with all information available that considers the gut microbiota as the holy grail and, related to that, probiotic drinks as the holy wine. We are far from knowing what the exact role of the microbiota composition and functionality is. However, the large amount of information available within scientific literature indicates that the gut microbiota, as part of an important digestive organ, might differently affect metabolism dependent on metabolic phenotype, age and gender. It is the task of the

scientific community to elucidate these differences, and investigate whether long term, but moderate dietary or lifestyle manipulations can positively affect body weight and metabolic profile in overweight and obese humans, and may beneficially alter related cardio-metabolic complications.

Concluding remarks

The study results as described in this thesis have been incorporated in original articles that have been published or submitted to scientific journals in the field of metabolism, diabetes and gastroenterology. These research articles are accessible to scientists who are interested in this topic. In addition, results have been presented at several (inter)national conferences to colleagues inside and outside the specific field, and have been discussed within the TIFN-framework with partners from industry. This study shows once again that care should be taken to extrapolate animal data to guidelines for humans, and that the human organism and its interaction with the environment is extremely complex.

References

1. Obesity and overweight Fact sheet N°3112015.
2. Hill JO. Understanding and addressing the epidemic of obesity: an energy balance perspective. Endocrine reviews 2006;27:750-61.
3. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nature reviews Molecular cell biology 2008;9:367-77.
4. Preiss K, Brennan L, Clarke D. A systematic review of variables associated with the relationship between obesity and depression. Obesity reviews : an official journal of the International Association for the Study of Obesity 2013;14:906-18.
5. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nature reviews Cancer 2015;15:484-98.
6. Naik R, Kaneda T. Noncommunicable diseases in Africa Population Reference Bureau; 2015.
7. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. Jama 2013;310:591-608.
8. Mikkelsen KH, Knop FK, Frost M, Hallas J, Pottegard A. Use of Antibiotics and Risk of Type 2 Diabetes: A Population-Based Case-Control Study. The Journal of clinical endocrinology and metabolism 2015;100:3633-40.
9. Kerr CA, Grice DM, Tran CD, et al. Early life events influence whole-of-life metabolic health via gut microflora and gut permeability. Critical reviews in microbiology 2015;41:326-40.
10. Ipsos MORI Veracity Index 2015: Trust in Professions United Kingdom: Ipsos Mori Market Research; 2015.